To: Robin Kinser

From: Barbara K. Zedler

Subject: KM: Recommendations for standardized format and standard items to include in study protocols, analysis plans, and reports

Date: July 22, 2003

STATISTICAL ANALYSIS

add RE adjusted values (2 methods)

1. Round calculated *p*-values to 2 decimal places when REPORTING them, unless < 0.01. For example, report < 0.0001 as < 0.001; report 0.0032 as 0.003; report 0.0892 as 0.09.

2. REPORT all calculated values to no more than 2 decimal places. If necessary, round calculated values with > 2 decimal places. If necessary for REPORTING meaningful yet manageable values, change the prefix (e.g., milli, micro, nano) of the fundamental measurement unit (e.g., liter, gram, mole).

3. Avoid calculating, modeling, and reporting biologically/scientifically irrelevant interactions/correlations (e.g., biomarkers vs. marital status/income/education level).

4. If the study analyzes a variable at multiple (> 1) time points, request descriptive statistics of the variable for the OVERALL period (averaged within each subject over all time points, then averaged over all subjects) as well as at each individual time point.

5. Reported analyses (e.g., demographic characteristics, AEs) should always include only evaluable subjects at the respective time point. Evaluable subjects are those who fulfill all study eligibility criteria for enrollment and continuation in the study and who have reportable results at Baseline and at least one time point after Baseline.

6. Demographic characteristics of interest always include: age, gender, race, BMI (preferred to weight), and, for the smokers, duration of smoking, number cigarettes per day (cpd), and Fagerstrom score (generally, present for the study groups by gender and overall).

7. Clearly specify in report involving analyses "by cigarettes smoked per day" HOW the number of cpd obtained, e.g., from returned pack count, from daily diary, from a specific questionnaire question).

8. 12. For short-term, confined studies where there are accurate daily cig consumption (cpd) records, there are four types of data:

- the original ("raw") data value
- the original data value adjusted for number of cigs smoked per day (cpd)
- % change from Baseline
- % change from Baseline adjusted for number cpd.

9. For long-term studies where there is unrestricted or ad lib smoking and no verifiably accurate daily cig consumption (cpd) records, there are two types of data:

- o the original ("raw") data value
- o the original ("raw") data value.

10. If "raw data" for a biomarker is determined to be invalid or biologically/scientifically implausible, do not manipulate it further (e.g., use in exposure-response modeling) or present it in the report narrative besides a description of the methodology and an explanation of the rationale for disregarding the results.

11. Subject each subject's 24-h urine collections on which biomarker data is based to a quality control procedure before accepting it [i.e., ensure adequacy of the collection by meeting minimum expected creatinine excretion levels and (for studies with multiple (> 1) 24-h urine collections) maximum inter-collection creatinine %CV levels].

CONTENT

1. **Present results in logical order and in a succinct, straightforward manner with minimal verbiage.** Use actual numerical descriptors whenever possible instead of vague terms, e.g., "68% of the subjects" rather than "the majority of the subjects".

2. **Avoid over-interpretation of the results**, especially with small sample size. Present the results in a straightforward quantitative manner with a simple interpretation (e.g., comparison of investigational product group with no-smoking group or comparator product group). Avoid the terms "seemed to", "appeared to", "tended to". Discussion of results belongs in a Discussion section (not in the Results section). Conclusions belong in a Conclusion section (not with the Results or Discussion).

3. The *Synopsis* should be just that: a succinct summary of the important results of the study. Be sure to cover all the study's stated Objectives.

FORMAT

1. Present all group comparisons in terms of the primary group of interest (usually the PREP group). For example, "(PREP) smokers had xx% less/greater (biomarker) levels/AEs/abnormal safety variables than non-smokers/(comparator) smokers". In tables, generally present the data for the primary group of interest first.

2. Use past tense consistently throughout. Active voice is preferred to passive.

4. In general, avoid the word "treatment" when the investigational product is a cigarette/smoking product rather than a drug/medication. Use "study group" or "group", not

"treatment group" as much as possible (exception is statistical ana section, where "group" has different connotation, and so "treatment" is generally unavoidable).

5. Use "urine" in common headers/graphic axis labels for COMBINED "24-hour", "first morning void", and "random" urine biomarkers. Use "blood" in common headers/ graphic axis labels for COMBINED "whole blood", "plasma", and "serum" biomarkers (i.e., rather than the more cumbersome term "blood/plasma/serum").

6. Present all data, Figures and Tables for each biomarker together and separate from other biomarkers. For example, group together all scatter plots, box plots and interaction plots for biomarker A, followed by a succinct interpretation, then present all data for biomarker B, etc. (rather than presenting all scatter plots for all biomarkers, then all box plots for all biomarkers, etc.).

7. Present all biomarkers in a consistent order throughout the report, generally all blood biomarkers, then all urine BMs, then all "other biomatrix" (e.g., exhalate, sputum, tissue) BMs.

8. Present data in tabular form as much as possible. Avoid narrative presentation of data unless very few data presented. For each figure or in-text table, always cite the table in the data listings which is the source of the data.

9. Use bulleted lists to improve readability of lists (e.g., study objectives, lists of biomarkers assayed, lists of assays done).

10. Preferred and/or correct terminology/spelling/formatting:
    - "subject", not "patient".
    - Use singular "Week" when used as an adjective for the noun "visit" (i.e., Week 2, 4, 6, and 12 visits), but plural "Weeks" when used as a noun (i.e., at Weeks 2, 4, 6, and 12).
    - Spell out state names (i.e., Virginia instead of VA).
    - Be consistent in EITHER spelling out OR using numerals for numbers (i.e., seven instead of 7).
    - "Urine mutagenicity" is the biomarker; "urine Ames test" is the assay. Ames test
    - Italicize *e.g.*, and *i.e.*,.
    - Italicize certain modifiers in chemical names: *epi-*, *trans-*, *cis*, *S-*, *N-*, *O-*.
    - Never capitalize *epi-*, *trans-*, *cis-*, hs (as in high-sensitivity), which means that, at the beginning of a bullet or sentence, where the first word is capitalized, instead capitalize the NEXT word (e.g., 8-*epi*-Prostaglandin..., 11-Dehydrothromboxane...).
    - high-sensitivity CRP, hs-CRP
    - 3-ABP-Hb adducts
    - NNAL-glucuronides, not NNAL-glucuronide
    - EHCSS Accord® JLI
    - Accord® Puff Activated Lighter™ (series JLI)
    - The topography device is the Clinical Research Support System *Micro* (CReSS micro™) made by Plowshare® Technology.
    - ClinQuick℠ SAS®

OTHER

1. Avoid study time point terms such as "initiation", "enrollment", "study participation", "prior to the study", "prior to study enrollment", "check-in" unless they are SPECIFICALLY defined elsewhere in protocol. These terms can be variably interpreted. It is simpler and clearer (and thus less likely to lead to inadvertent protocol violations) to use "Screening", "Day -1", "Day -3", or even "confinement". Capitalize "Baseline", "Day", "Screening" if referring to a SPECIFIC defined time point in the study.

2. Include a section for *Abbreviations, Definitions, and Calculations.* Include study terms with a study-specific meaning that may be misinterpreted by the reader without the intended meaning defined (e.g., controlled, uncontrolled, unrestricted, ad lib smoking; Enrollment, Screening, Baseline, Acclimation Days).

3. Include a comprehensive electronic TOC that includes **all** sections on the CD-ROM.

4. Determine a "scientific point person" at the entity that will be writing the study report to have scientific oversight of the results (i.e., scientific interpretation and discussion) and to be liaison with sponsor to address issues/questions that arise.

5. Specify the material of all sample/specimen containers, including lids if that is important (i.e., HDPE, HDPP).

6. List exploratory analyses under "Other Objectives" (instead of Primary and Secondary Objectives).

7. Amendments to the protocol, attachments or ICF require IRB approval and Sponsor signature before implementing. Administrative changes (that do not directly affect the subjects) are sent in a letter (LOAC or NTF) to the IRB for receipt and review, but do not require IRB approval.

8. To minimize errors, confusion, and redundancy, **all** communication regarding a study (esp to external vendors/CRO/IRB but also to internal PM support groups) to go via (to/from) the study manage.